Role of Steroids and vasopressors in ICU

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Shock is a medical emergency characterized by hypotension and decreased tissue perfusion which if left untreated can lead to irreversible tissue injury and death.

Drugs commonly used for the treatment of shock are adrenergic agents like dopamine, dobutamine, epinephrine and norepinephrine. In recent years, vasopressin has been increasingly used due to its potent vasopressor effects.

The use of corticosteroids as an adjunctive therapy has been controversial for decades. Acute adrenal insufficiency is manifested as shock that is poorly responsive to fluids and vasopressors like in cardiogenic and septic shock. The rationale for therapy with corticosteroids at dose of 200-300 mg of hydrocortisone per day originated in the observations that patients with septic shock who had reduced response to corticotropin were more likely to die and that the pressor response to noradrenaline may be improved by hydrocortisone administration. Current recommendations based on 5 trials involving 464 patients suggest treatment of patients with septic shock with physiologic doses of hydrocortisone. Metaanalysis of these trials suggested that use of corticosteroids reduced mortality.

Clinicians make an initial choice of vasopressor based on published guidelines, individual experience and institutional bias.

CAUSES OF SHOCK
1. Cardiogenic
2. Hypovolemic
3. Obstructive

TREATMENT OF SHOCK
Cardiogenic shock  
Dobutamine  
NE  
Epinephrine  
Phosphodiesterase inhibitors - amrinone/milrinone

Hypovolemic shock  
- Fluid resuscitation

Obstructive shock
Outflow problems  
Judicious fluids  
Inotropes or mixed inotropes / vasoconstrictor  
Dobutamine, NE

Inflow problems  
Fluids  
Relieve source - chest tube, pericardiocentesis

Medication induced shock  
Neuraxial blockage - phenylephrine

Impairment of normal flow of blood  
- obstruction of outflow  
  PE, pulmonary HT, severe AS  
- obstruction of inflow  
  cardiac tamponade, pneumothorax  

4. Medication effects  
Neuraxial local anesthetics  
Systematically active drugs

5. Distributive shock  
Low vascular tone, increased vascular capacitance  
- Sepsis  
- Acute adrenal insufficiency  
- Neurogenic shock
Systemic vasodilators - phenylephrine or NE
Cardiac depressants
Inotropes dobutamine
NE contraindicated if concomittent vasodilatation

**Septic shock**

**Agents - NE**
- Dopamine
- Vasopressin
- Phenylephrine
- Dobutamine
- Adrenaline

**Problems with vasopressors**

**Dopamine**
- Tachyphylaxis
- Failure to release NE in v/o depletion of NE in shock states leading to lack of vasopressor effect

**Noradrenaline**
- Extravasation can be problematic

**Dobutamine**
- Tachydysrhythmias
- Hypotension can occur 2° to β2 effects

**Vasopressin**
- Reduced GI blood flow, even at low dose
- Cardiac ischemia

**RECENT TRIALS**

Few recent trials are presented here.

To evaluate the efficacy and safety of low dose hydrocortisone therapy in pts with septic shock (CORTICUS). NEJM 2008, 358 : 111-124.

**Design** - Multicenter, prospective randomized double blind placebo controlled trial. 50 mg IV hydrocortisone every 6h x 5d period Vs Placebo.

**Result** : Hydrocortisone did not improve survival in pts with septic shock. However hydrocortisone hastened reversal of shock in all study patients.

**Comments**

Corticus - largest trial of corticosteroids in patients with septic shock but was still inadequately powered to detect a clinically important treatment effect. Corticotropin stimulation test does not identify pts who will benefit from corticosteroids. Rapid reduction in the need for vasopressors is an unreliable surrogate outcome since it does not predict survival. More studies needed.

Hydrocortisone cannot be recommended as general adjuvant therapy for septic shock (Vasopressor responsive), nor can corticotropin testing be recommended to determine which patients should receive hydrocortisone therapy. Hydrocortisone may have a role among patients who are treated early after the onset of septic shock who remain hypotensive despite the administration of high dose vasopressors (vasopressor unresponsive).


**Dopamine Vs NE in treatment of shock**

**Design:** Multicentre randomized trial.

Dopamine or NE as first line vasopressor therapy to restore or maintain blood pressure when unable to maint BP with maximal dose of dopamine (20 microgm/kg/min) or norepinephrine (0.19 microgm/kg/min) Epinephrine or vasopressin could be added.

**Primary outcome:** Rate of death at 28 days after randomization

**Secondary end point:** No. of days without need for organ support and occurrence of adverse events.

**Results:** Total patients 1679; Dopamine - 858; Norepinephrine - 821. No significant difference in rate of death at 28 days. More arrhythmias in dopamine group.

Subgroup analysis showed that dopamine was associated with an increased rate of death at 28 days among 280 patients with cardiogenic shock but not amongst 1044 patients with septic shock or 263 with hypovolemic shock.

**Conclusion:** Although there was no significant differences in rate of death between patients treated with dopamine and NE, use of dopamine was associated with greater number of adverse events.

This study raises serious concerns about the safety of dopamine as compared to noradrenaline.


450 pts with septic shock; 73% recd NE 50.5% recd DA

**Outcome:** NE associated with worse outcome. NE is an independent risk factor for the mortality in septic shock.


**Hypothesis:** Vasopressin in low doses may decrease morality in septic shock. Randomized multicentre controlled trial involving 778 patients with septic shock. Low dose vasopressin added to norepinephrine vs norepinephrine
alone were compared.

**Outcome:**
Overall no reduction in 28 day / 90 day mortality. No significant differences in adverse effects

**Comments:**
Although adding vasopressin to norepinephrine therapy in patients with septic shock appears to produce similar mortality rates and is safe. There is no compelling advantage to using vasopressin rather than norepinephrine. Thus it is the timing of the vasopressor and other therapy rather than the specific agent which matters in shock.

**Recommendations about vasopressin**
1) To be used in patients with septic shock that are in mid range dose of NE (5-15 microgm/min)
2) Patients who develop tachyarrhythmia on NE
3) Patients with extreme acidosis
4) Patients on very high doses of NE
5) Peri cardiopulmonary bypass and CPR

**European study - Epinephrine vs Norepinephrine + dobutamine.** Lancet 2007 (25 ) 370 (988) : 676-84
Epinephrine vs. norepinephrine (NE) + Dobutamine (DA). 330 pts with septic shock. Randomized trial. No significant difference in mortality/serious adverse events.

**Dopamine:** Septic occurrence in acutely ill patients. Hypotension - Dopamine worsens outcome in shock.

**Design:** observational study in 198 ICUs. Subjects - 1058 pts with shock.

**Outcome:**
DA and NE used more in non survivors.
DA is an independent risk factor for mortality in pts with shock and in subcategory of pts with septic shock. Crit care Med 2006; 34(3); 589-97

Intensive care is assuming increasingly important role within the hospital. Although patient outcomes are steadily improving there is still a scope to effectively manipulate physiology, biochemistry and immunology to achieve better results.

The results of multi centre studies may not give clear cut answers but draw attention to several issues and improve the understanding.

There is always a need for critical appraisal to modify clinical practice on basis of available evidence rather than blindly follow guidelines.

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